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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,359	03/14/2001	Nobuchika Yamamoto	204415US0PCT	5873

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EXAMINER
CHISM, BILLY D

ART UNIT	PAPER NUMBER
1654	7

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/786,359	Applicant(s) YAMAMOTO ET AL.	
	Examiner B. Dell Chism	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☒ Claim(s) *1-4 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office Action is responsive to Paper Number 6, filed 31 October 2002, wherein Applicants traversed the Lack of Unity requirement of Paper Number 5, submitted 30 September 2002, by the Examiner. Upon reconsideration of the restriction requirement and the reasoning of the Applicants, the Examiner withdraws the restriction requirement and considers the application fully on the merits.

Claim Objections

1. Claims 1-4 objected to because of the following informalities:

Claim 1 should read "an MMP-production inhibitor."

Claim 2 should read, "is a macrolide[s]." Appropriate correction is required.

Claim 2 should not read on the "use of claim 1", claim 2 should read on the immunosuppressant of claim 1, i.e., "The MMP-production inhibitor of claim 1 wherein the immunosuppressant is a macrolide of the following formula (I)."

Claim 3 does not have an article (A) at the beginning of the claim.

Claim 4 has "inhibiting a production", but the "a" should be deleted or removed to read "a MMP".

2. Claim 9 is objected to under 37 CFR 1.75(c) as being in improper form because a claim must be drawn to either a composition or to a method, but it cannot be a hybrid claim drawn to both a composition and a method (as well as not reciting any actual limitations) and should not be further treated on the merits. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1,3-7 are rejected for the indefinite recitation of the acronym "MMP" wherein the Applicants should first give the full wording represented by the acronym and with the acronym, and use the acronym thereinafter.

Claims 1-2 and 5 provide for the use of a MMP-production inhibitor, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicants is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-2 and 5 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 2 is indefinite in the last portion of the claim where it recites "in addition to the above definitions..." The claim is unclear as to what above definitions. Furthermore, claim 2(b)

is indefinite where it says, "may form another bond formed..." It is unclear as to which bonds the claim is referring.

Claim 4 is rejected for the indefinite recitation of the phrase "a production of MMPs," wherein the "a" should deleted from the claim.

Claim 4 is rejected for being indefinite wherein it is unclear as to what the administration is on and/or in. For example, is the method for administering to a patient, mammal and/or human?

Claim 8 is rejected wherein the claim appears to be a product claim reading on what appears to be a method claim of claim 1.

Claims 10-11 are rejected for depending from rejected claims 6 and 7 respectively.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of tacrolimus and 33-epi-chloro-33-desoxyascomycin or pharmaceutical compositions thereof for the treatment of MMP-mediated diseases, does not reasonably provide enablement for the use of cyclosporin A or the pharmaceutical compositions thereof for the treatment of MMP-mediated diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same..." The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to compositions and uses of immunosuppressants for the treatment of MMP-mediated diseases, wherein the

immunosuppressants are tacrolimus or 33-epi-chloro-33-desoxyascomycin (each are compounds fitting general formula I), however, the claimed use of cyclosporin A as the immunosuppressant is not enabled in the disclosed teaching of the specification.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the use of cyclosporin A and tacrolimus is not predictable, as the two immunosuppressants can and do act differently on different hormonal systems and cell types (Milad *et al.* 1995. Interaction of the Progesterone Receptor with Binding Proteins for FK506 and Cyclosporin A. Molecular Endocrinology 9: 838-847).

The amount of direction or guidance present and the presence or absence of working examples: Given the teachings of unpredictability found in the art regarding the effects of the two different compounds of cyclosporin A and tacrolimus, detailed teachings are required to be present in the specification to enable the skilled artisan to use the claimed immunosuppressants and/or the compositions thereof. These teachings are absent. The specification makes general statements that the claimed cyclosporin A is useful as for the treatment of MMP-mediated diseases; however, it fails to teach how to use the cyclosporin A pharmaceutical composition could be used for treating MMP-mediated diseases. There is no guidance as to how to overcome the teachings of unpredictability that are found in the art.

The breadth of the claims and the quantity of experimentation needed: Because the art teaches the unpredictability of cyclosporin A and tacrolimus or a compound of formula (I)and because the disclosure does not contain sufficient teachings to overcome the unpredictability taught in the art, one of skill in the art would not be able to use the claimed invention absent undue experimentation.

7. Claims 5-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of tacrolimus and 33-epi-chloro-33-desoxyascomycin for treatment, does not reasonably provide enablement for use of tacrolimus and 33-epi-chloro-33-desoxyascomycin for prevention of MMP-mediated diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case, applicants are claiming a composition that is an agent for "preventing" MMP-mediated diseases. The nature of the invention is use of a pharmaceutical for the treatment of a disease, i.e. arthritis. As stated, however, the claims assert that the composition is capable of preventing MMP-mediated diseases, or to keep from happening. The state of the art does not teach the absolute prevention of MMP-mediated diseases, merely that the symptoms of the disease, such as basement membrane matrix metabolism (specification page 15), may be treated. Thus any claim to the prevention of MMP-mediated diseases is highly unpredictable given the current state of the art. Furthermore, applicants do not provide examples as such. Whereas examples are given for the amelioration of MMP-mediated diseases, prevention is not

taught. Because neither the prior art nor the current application provide sufficient guidance to one of even ordinary skill in the art as to the prevention of MMP-mediated diseases, the quantity of experimentation for such a claim is considered to be undue and thus, not enabled.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 3-4 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Gottschall, P.E., 1996, (Neuroreport 7(18):30-77-3080). The claims teach the use or method of using an immunosuppressant as a MMP-production inhibitor, and the use of an immunosuppressant with a carrier or excipient. The art (Gottschall, 1996, see abstract and p. 3079 column 1) teaches the use of the anti-inflammatories indomethacin (INDO) and/or dexamethasone (DEX) for the inhibition of MMP-9 production by beta-amyloid induction. Although claims 1, 3-4 and 7 are intended to be drawn to macrolides of formula (I) and cyclosporin A, the claims are broad in the general form, thus encompass any immunosuppressant shown to inhibit MMP production. Applicants can obviate this rejection by narrowing the independent claims to those compounds and/or compositions properly described and enabled by the specification.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to B. Dell Chism whose telephone number is 703-306-5815. The examiner can normally be reached on 7:30 AM - 4:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

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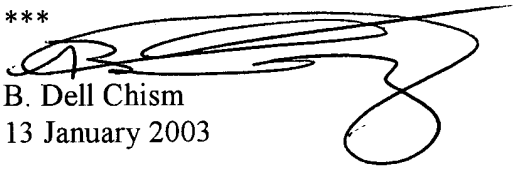

B. Dell Chism
13 January 2003